ASGCT 20th Annual Meeting
Washington, DC • May 10-13, 2017

Clinical and Operational Infrastructure for Engineered Cell Therapy Delivery

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Assistant Medical Director Cell Manipulation Core Facility

May 9th, 2017

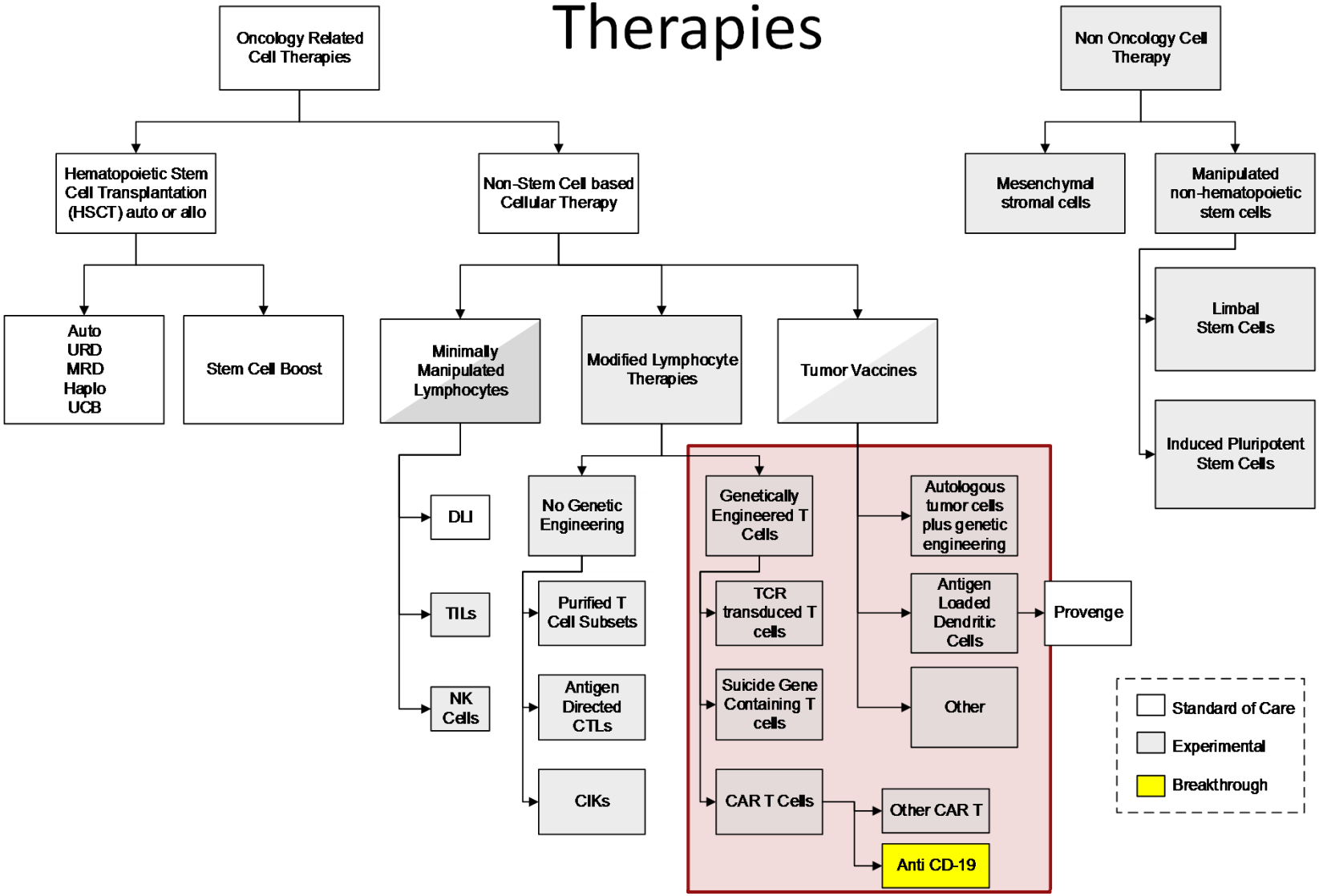
Relevant Disclosures

- Several Advisory Boards for Kite Pharma

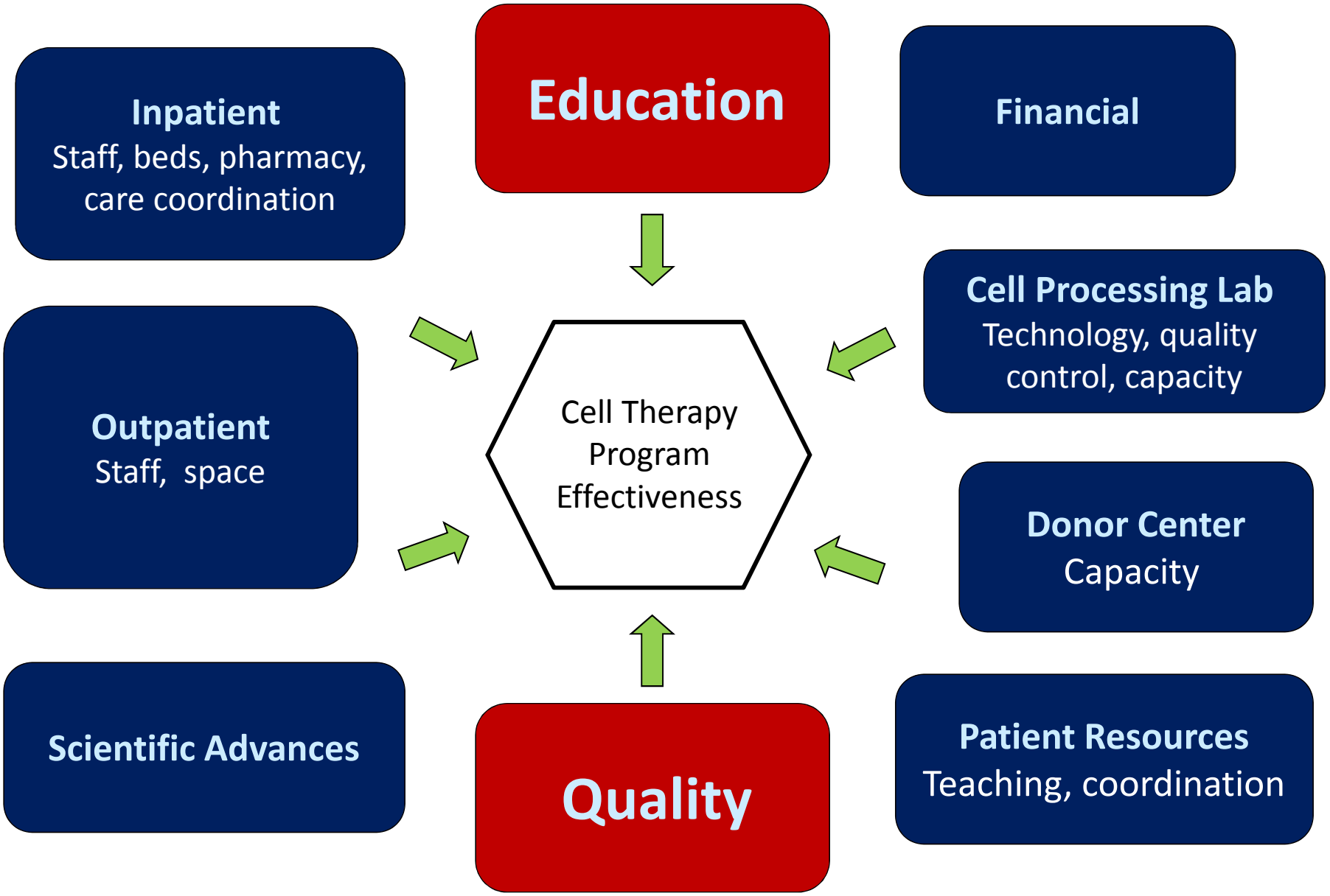
Outline

- Implementation tips – any cellular therapy
- Clinical/manufacturing interface - specific to newer engineered cellular therapies
- Institutional model to deliver safe quality products and care
- Examples and case studies

Basic Scientific Overview | Taxonomy of Cell Therapies



Coordinated Planning & Effort is Essential for Cellular Therapies



Any Cellular Product - Collection

- Get the initial product you need
  - Additional additives (plasma)
- Processing stipulations
  - Number of bags frozen
  - Cell dose
- Deliver the products you want
  - Choosing from inventory
- Triple check

Track What You Do

- Process Characteristics
- Calculations
- Dates times
- Cell Infusion Reactions

Communicate, Communicate (Educate, Educate!!!)

- Preview records and ask clinicians/program RNs
- Lab-wide distribution lists for follow-up/alerts
- Standardized times and handoffs to nursing
- Document

- Patient full name and DOB

- MRN and floor location

- Planned Day 0 and anticipated timing to floor

- Type of product and manipulation performed

- Volume of product and any DMSO

- Any special concerns, name of tech for future ?s

- Next planned communication with CMCF

Example 2 "I'm calling about a product coming from the CMCF on patient Adam Smith, DOB 1/1/70 BWH number 11100011 on floor 6A.

We received a **fresh allogeneic marrow product** last night and are starting RBC depletion with an anticipated **delivery to floor at 6pm** today.

We expect the final volume to be around **600cc**. There will **be no DMSO**.

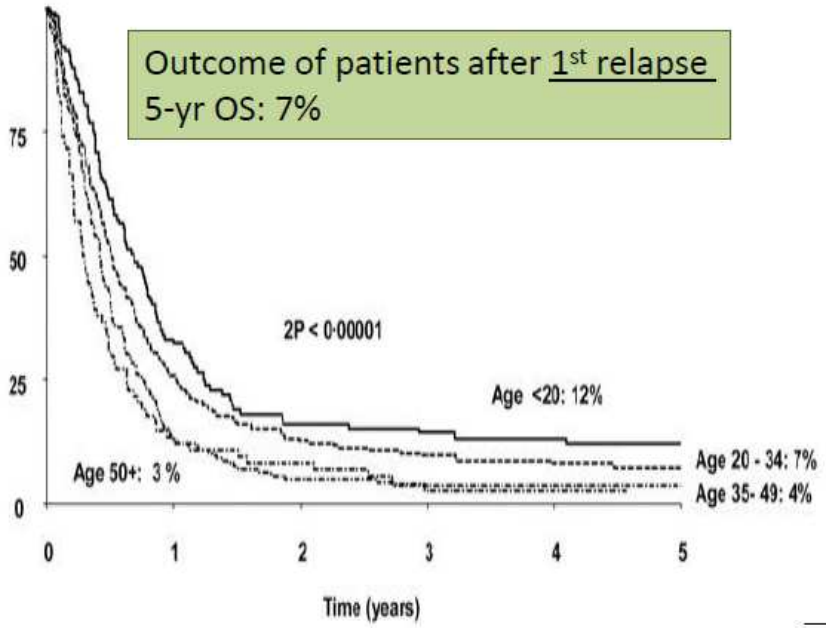
We received word from the NMDP that initial OR samples on this product grew **gram positive cocci** within 24 hours of collection. Our assistant medical director is in contact with the MDs responsible to discuss and you should contact the primary team with any ?s on how that is impacting the infusion.

My **name is Jack** and I am reachable at 632-5767. I am not sure who will be responsible for the product at time of delivery but you can **ask for Brian** who will be able to get you information at that time.

The **next call from the CMCF** will be around 5pm to confirm actual time of delivery."

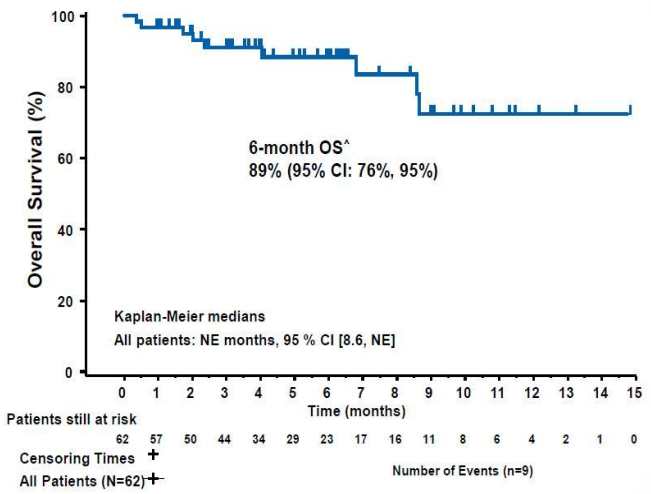
And Then It Gets Interesting!!

MRC UKALL2/ ECOG2993 Study (n=609)

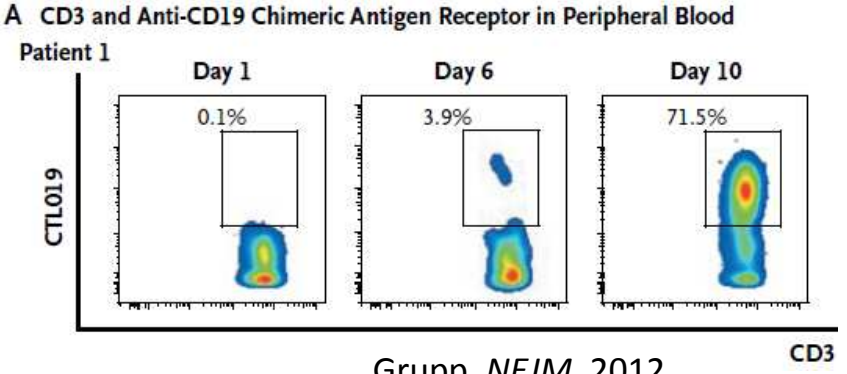


Fielding A, et al. *Blood* 2007;109(3):944-950.

ELIANA: Overall survival (OS)



^Full analysis set
All patients infused with CTL019 were included. Time is relative to CTL019 infusion

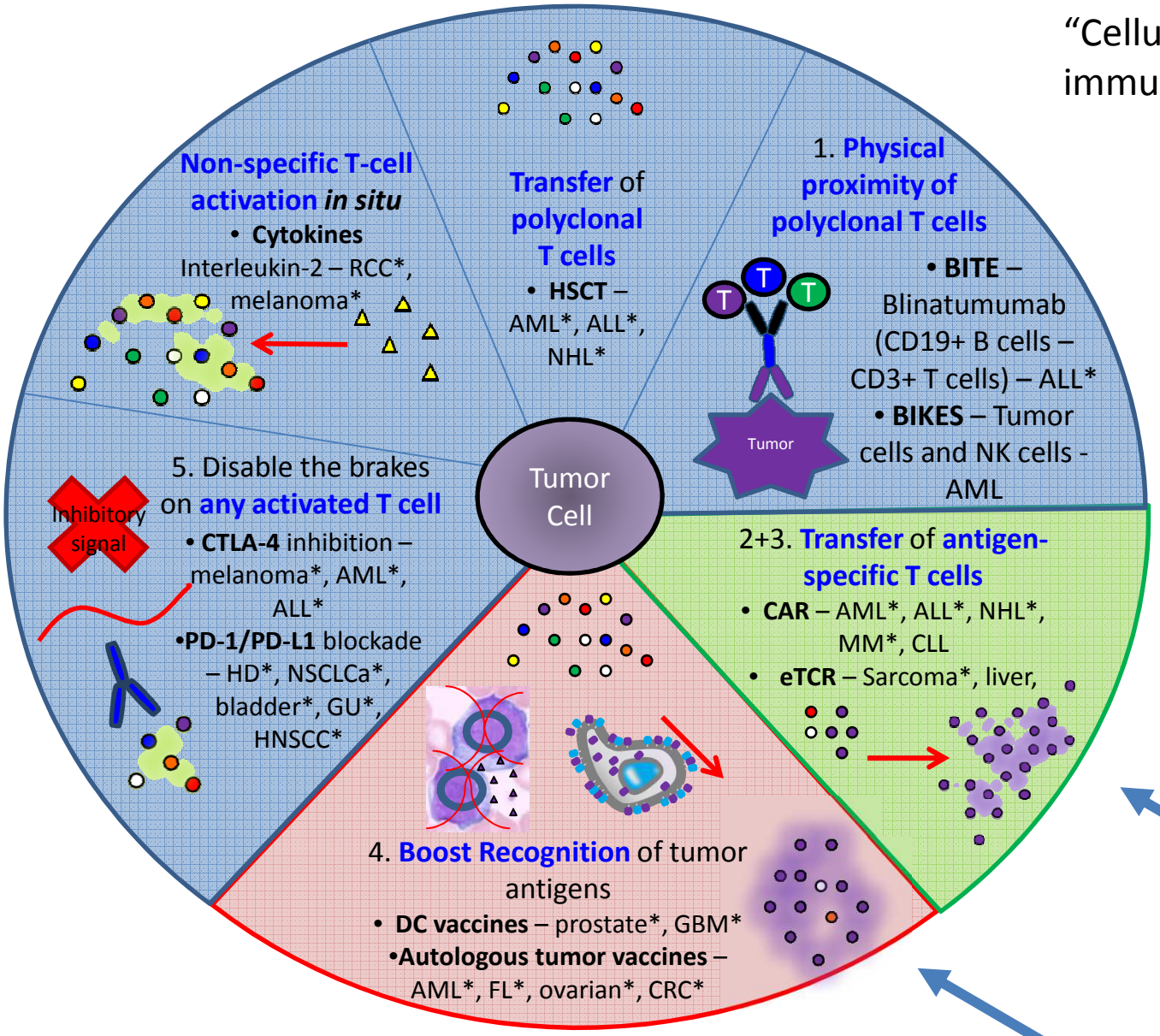


Grupp, *NEJM*. 2012

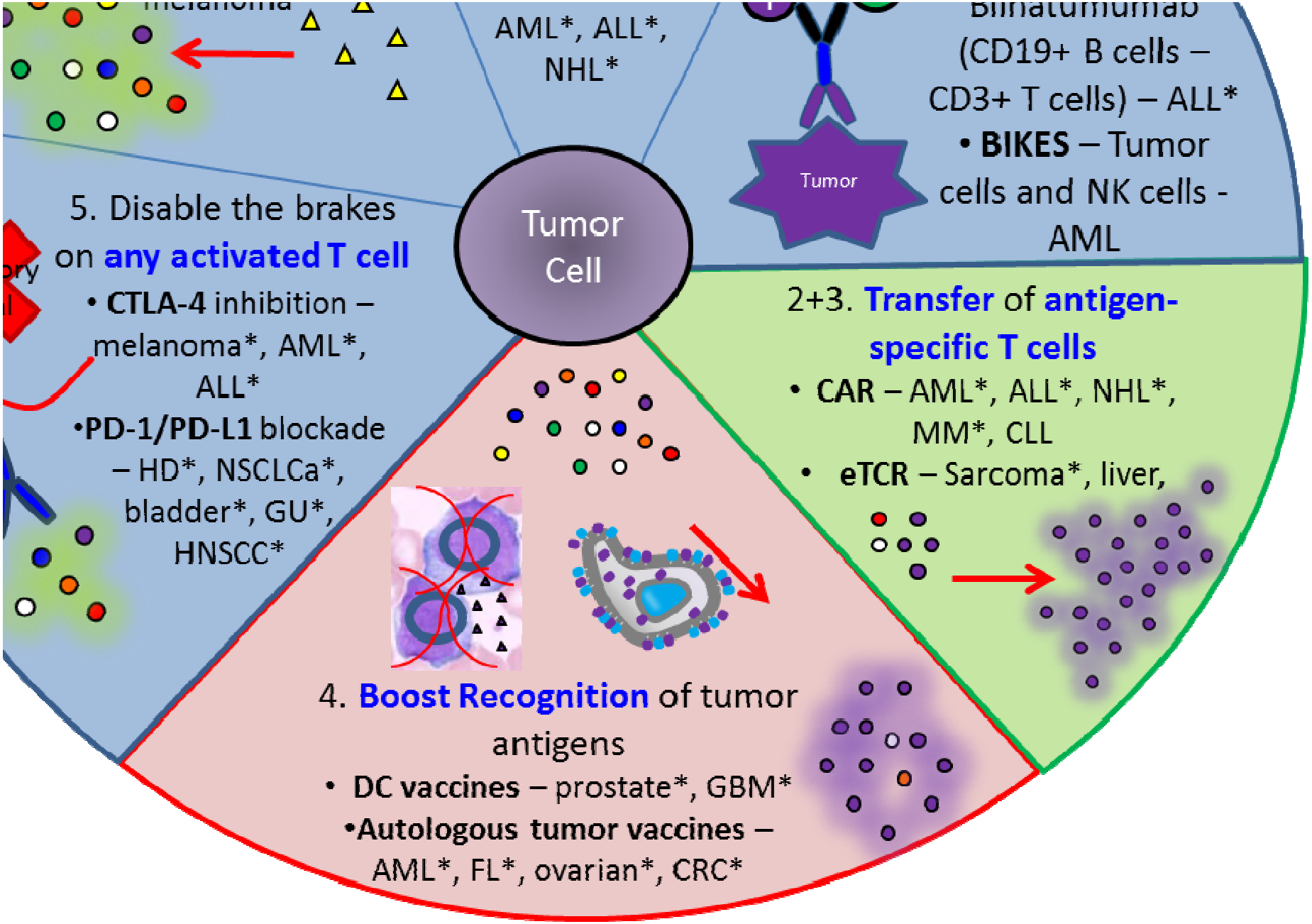
Newer Engineered Cellular Therapies

- Exploding!!
- Invigorating clinical results with CD19 CARs
- Proliferation of genetic engineering and antigen recognition techniques
- Different modalities of cancer immunotherapy are feeding each other

How to Optimally Harness Anti-tumor Immunity

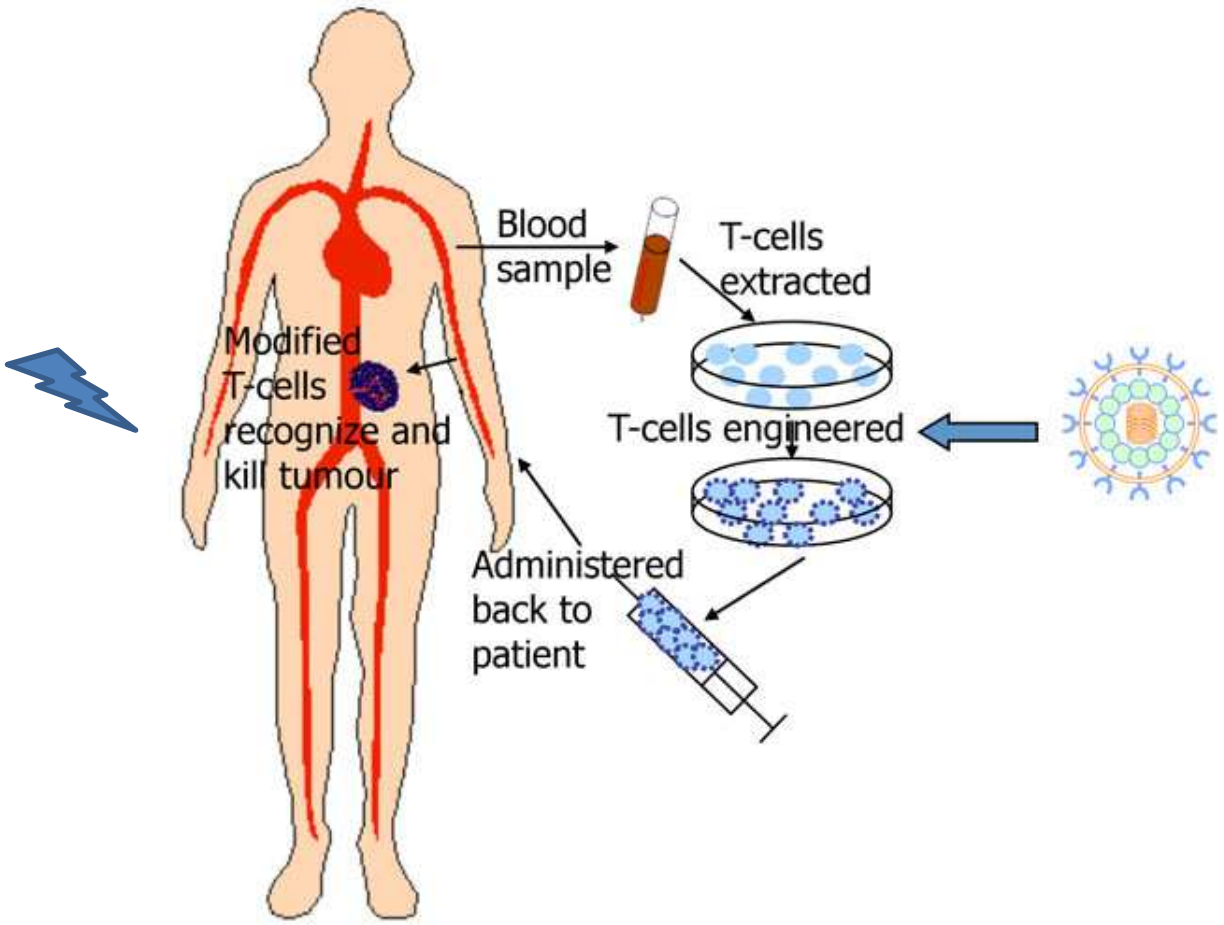


"Cellular" immunotherapy


AML*, ALL*, NHL*
Blinatumumab (CD19+ B cells – CD3+ T cells) – ALL*
• BIKES – Tumor cells and NK cells - AML
Tumor
Tumor Cell
5. Disable the brakes on any activated T cell
• CTLA-4 inhibition – melanoma*, AML*, ALL*
•PD-1/PD-L1 blockade – HD*, NSCLCa*, bladder*, GU*, HNSCC*
2+3. Transfer of antigen-specific T cells
• CAR – AML*, ALL*, NHL*, MM*, CLL
• eTCR – Sarcoma*, liver,
4. Boost Recognition of tumor antigens
• DC vaccines – prostate*, GBM*
•Autologous tumor vaccines – AML*, FL*, ovarian*, CRC*

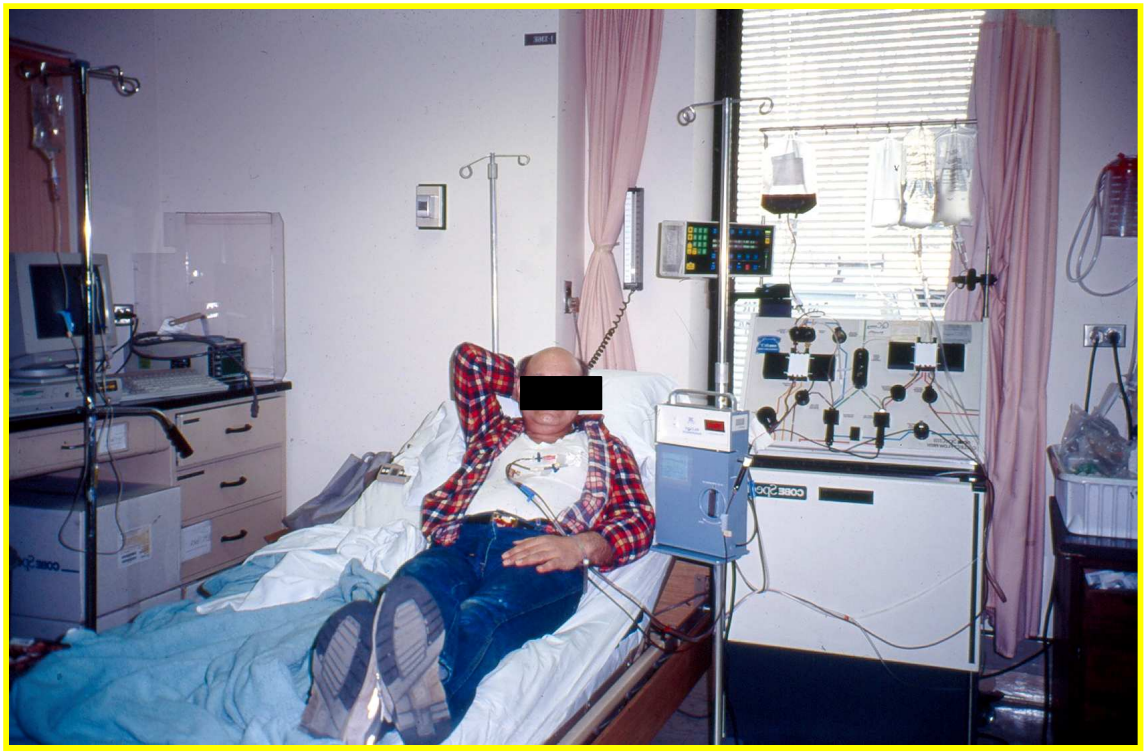
Autologous Product Manufacture Process

- Antigen-Directed T cells
  - Chimeric Antigen Receptor T cells
  - Engineered T-cell Receptors



Donor Collection Process - Apheresis

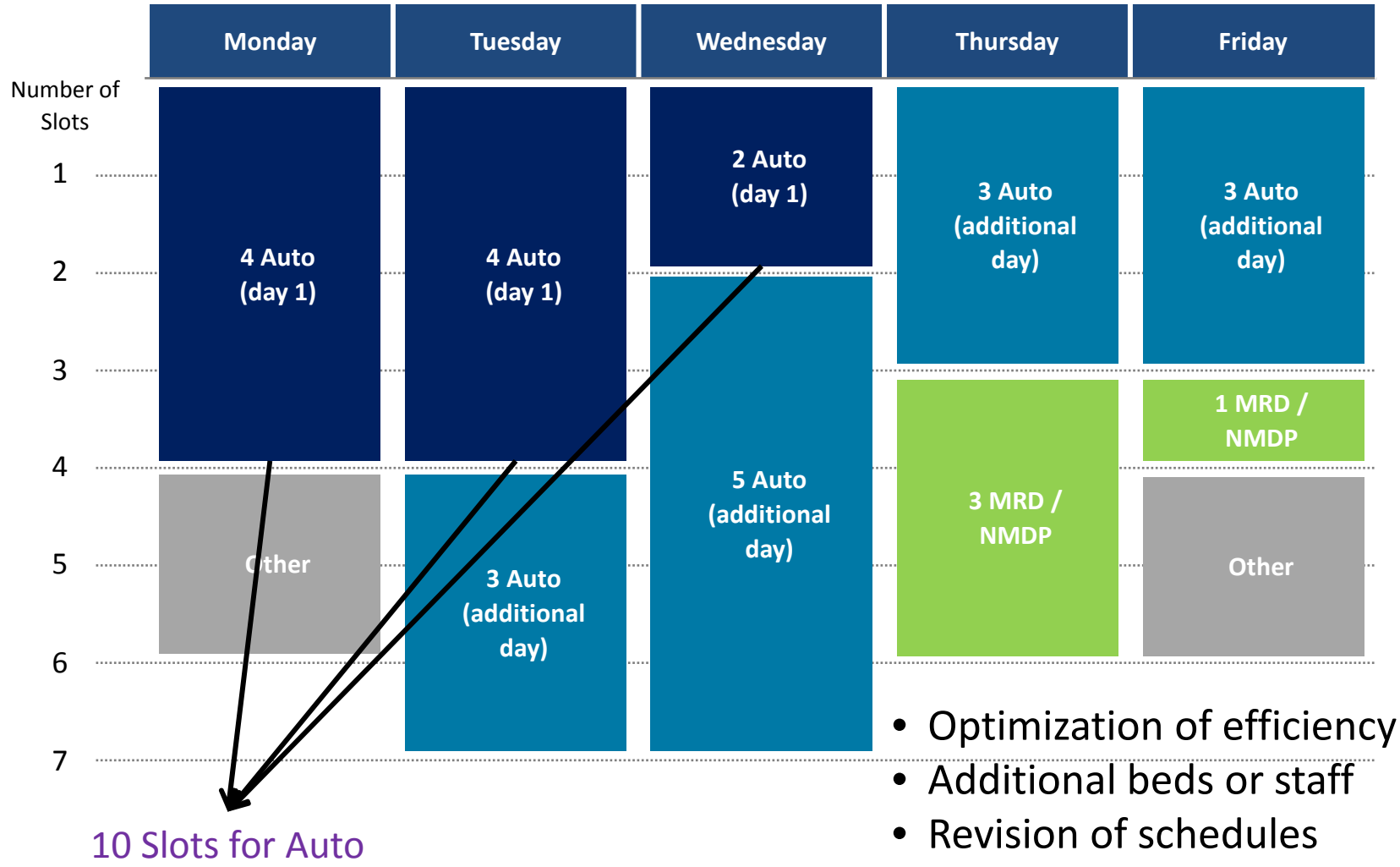
- Do all clinical sites have affiliated apheresis facilities?
- How is chain of custody and chain of identity established?
- Does the apheresis site have the bandwidth to accommodate volume?



?? Additional Merits of Allogeneic 3rd Party CAR T Cells ??

2015 Apheresis Schedule

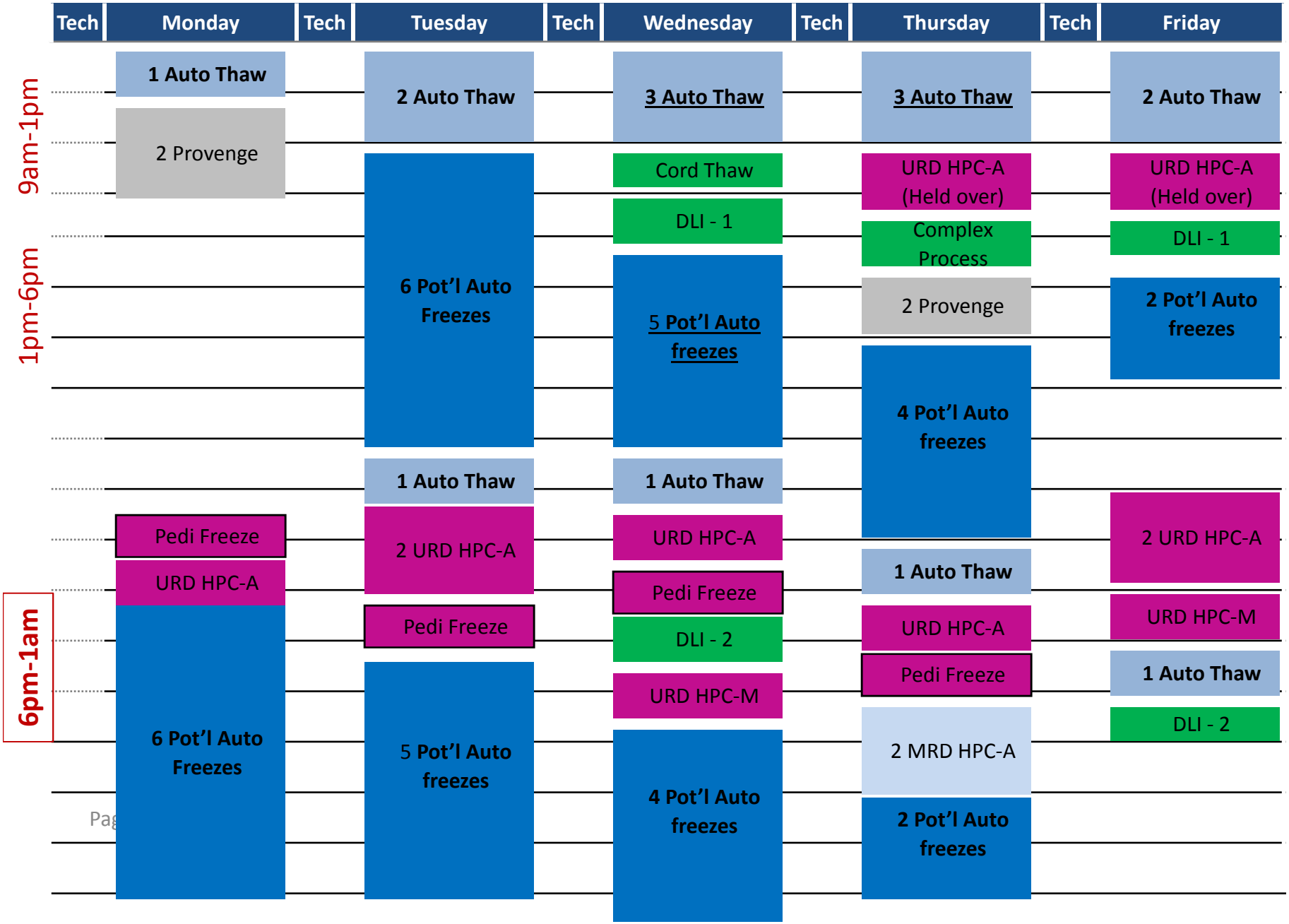
Weekly Available Apheresis Slots



- Optimization of efficiency
- Additional beds or staff
- Revision of schedules
- Restriction of limited resources
- Centralization of scheduling

Source: Donna Crown

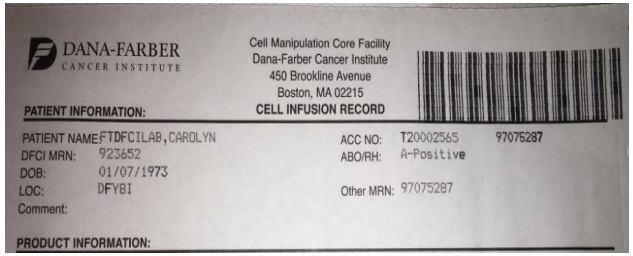
Sample CMCF Processing Schedule



Key Areas for Clinical Delivery

- Cell collection and distribution – COC, COI, labeling
- Trial initiation
- Communication, training, and clinical care
  - MDs, RNs
  - ICU
  - Emergency room
  - Pharmacy
- Resource utilization
- Safety and outcome monitoring
- Financial structures

Chain of Custody and Identity – FACT, AABB, JC



DANA-FARBER CANCER INSTITUTE

Cell Manipulation Core Facility
Dana-Farber Cancer Institute
450 Brookline Avenue
Boston, MA 02215
CELL INFUSION RECORD

PATIENT INFORMATION:

PATIENT NAME: FTDFCILAB, CAROLYN
DFCI MRN: 923652
DOB: 01/07/1973
LOC: DFY8I
Comment:

ACC NO: T20002565 97075287
ABO/RH: A-Positive
Other MRN: 97075287

PRODUCT INFORMATION:

W1221 16 123123 8 G

4700

O
Rh Positive

Brigham & Women's Hospital
Boston, MA
FEI# 0001277447

Collection Date/Time 0161611312
09 Jun 2016 13:12 EDT
(09 Jun 2016 17:12 UTC)

Do Not Irradiate
Do Not Use Leukoreduction Filter

S2847490 DESIGNATED
HPC, APHERESIS
Mobilized, CD34 enriched

See Attached Documentation for Details
Total Volume 99.5 mL

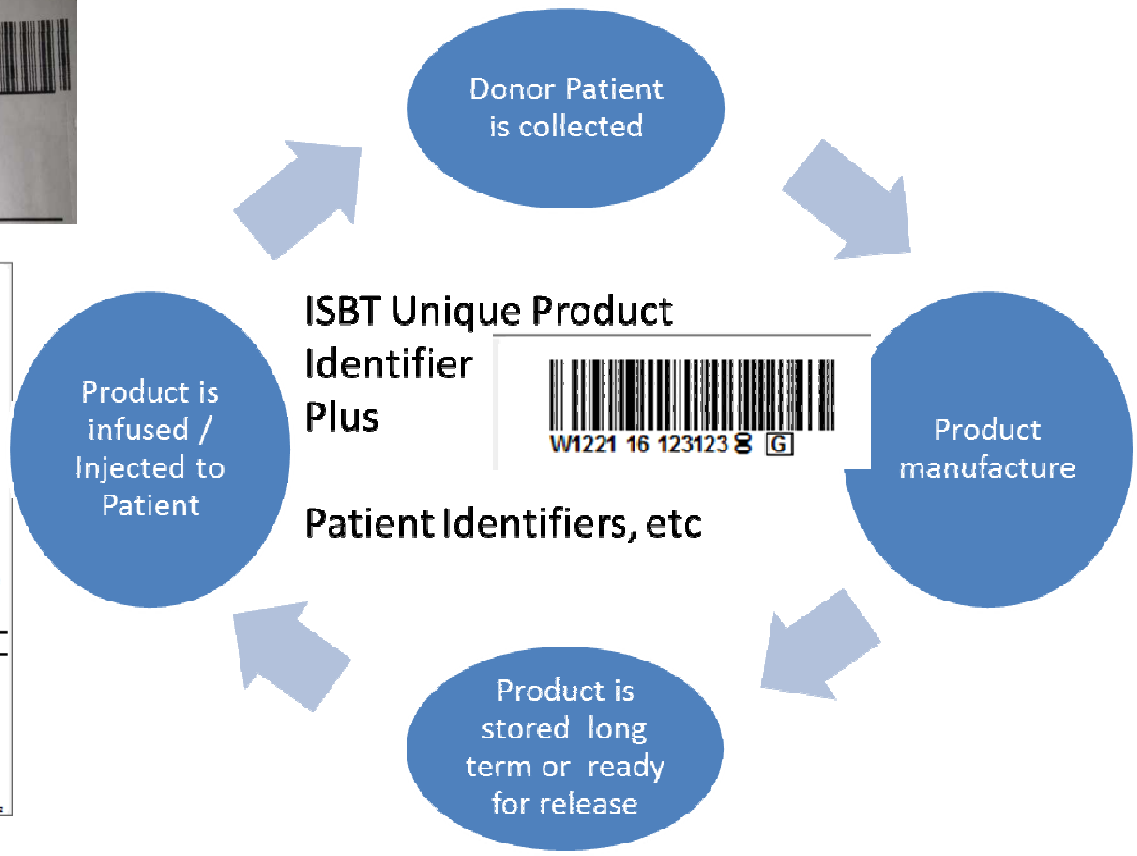
Store between 20 to 24 C
Part: B0

For Use by Intended Recipient(s) Only
Unrelated Donor
Donor ID: 1234-5678-9

0161631312 Expiration Date/Time
11 Jun 2016 13:12 EDT
(11 Jun 2016 17:12 UTC)

Intended Recipient
FTDFCILAB, CAROLYN
Recipient ID: BWH 97075287

CMCF Dana-Farber Cancer Institute
450 Brookline Ave Boston MA 02215
FEI# 3003934255

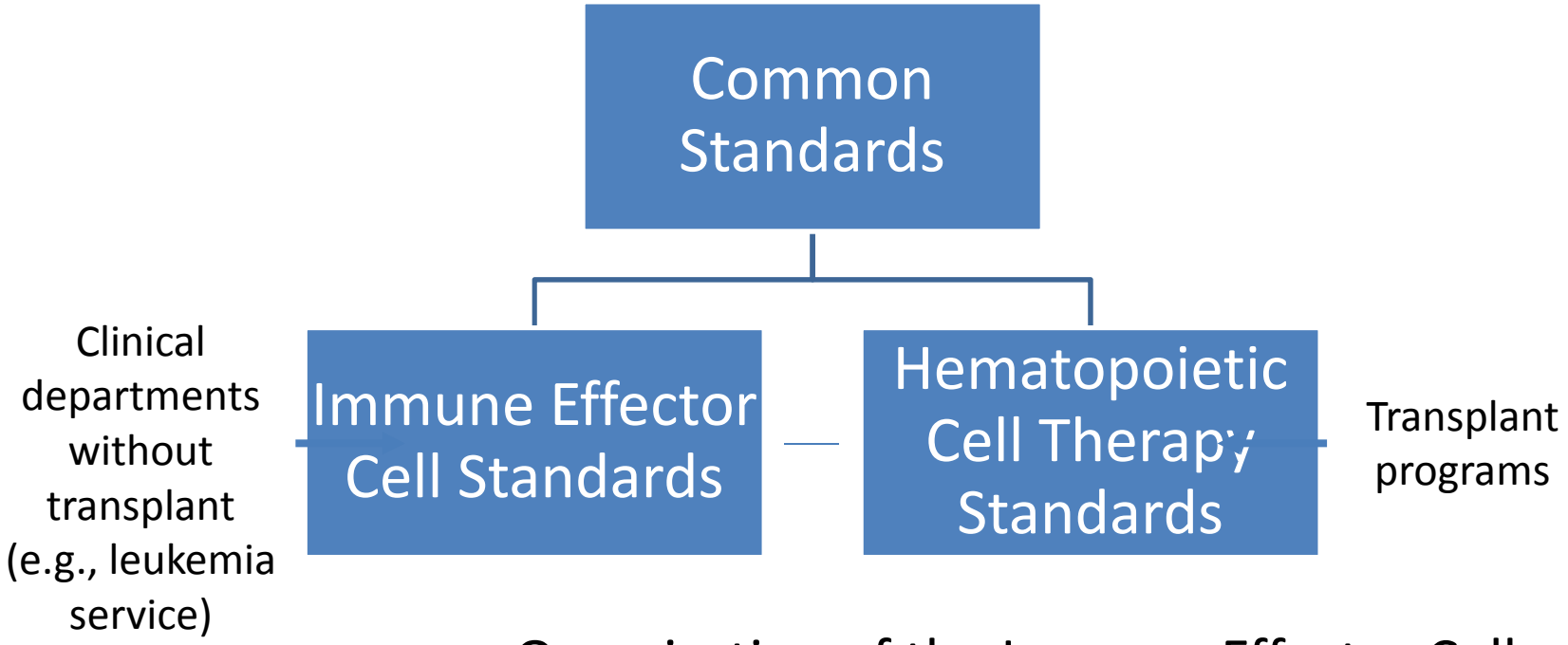


Scope of Immune Effector Cell Standards

- Cells used to **modulate an immune response** for therapeutic intent
  - May elicit a response or mitigate a response
  - Cell types include **dendritic, natural killer, T, and B**
- Common products
  - Chimeric antigen receptor T cells (**CAR-T cells**)
  - Therapeutic vaccines
- Guidance on processes – not science
  - Donor selection and management, collection, administration of cells, management of adverse events, and evaluation of clinical outcomes
  - Quality Management (QM) program

Foundation for the Accreditation of Cellular Therapy

FACT Common Standards as the Starting Point



- Organization of the Immune Effector Cells: accommodating different models of care

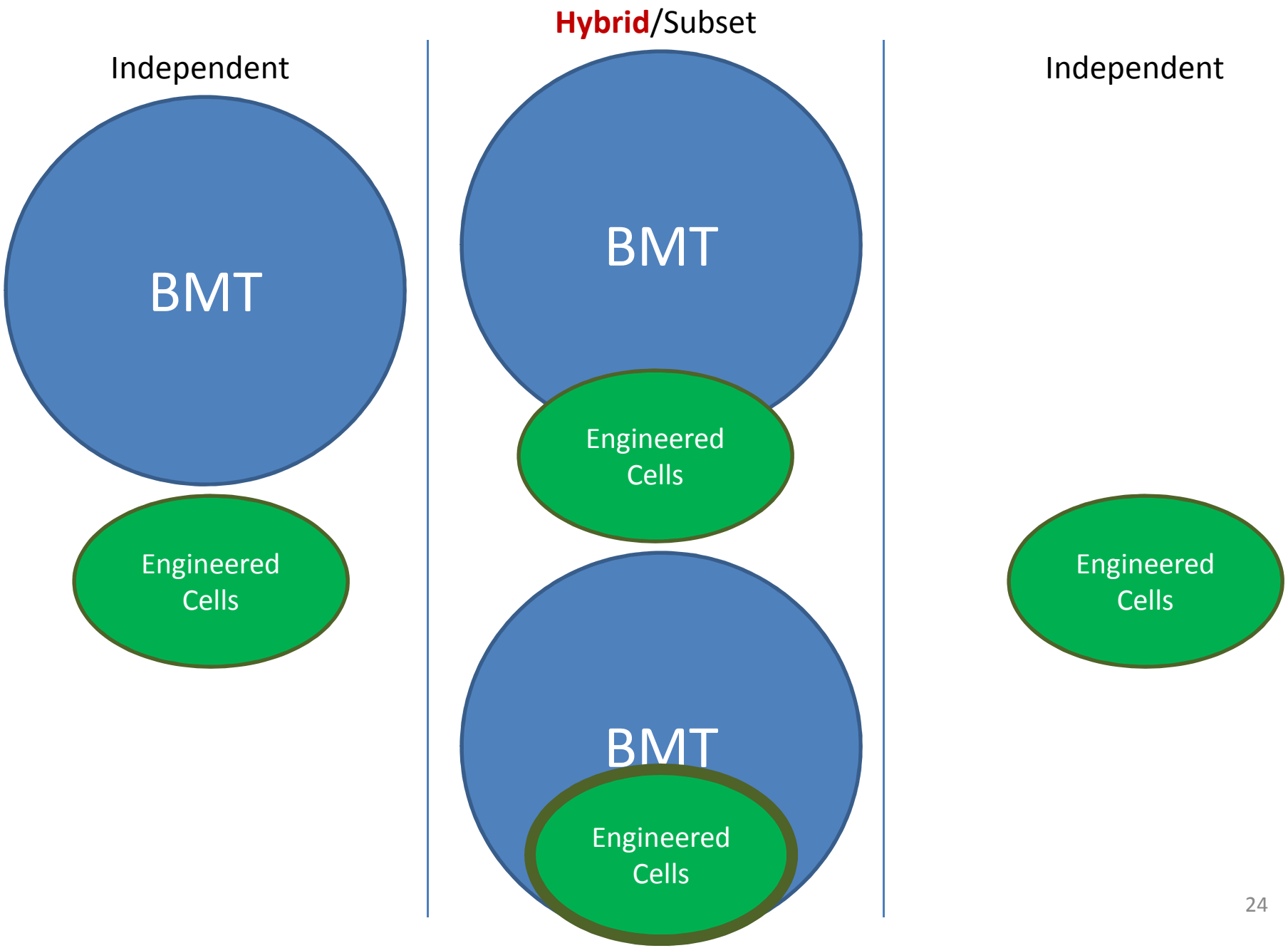
Foundation for the Accreditation of Cellular Therapy

Requirements for Immune Effector Cells

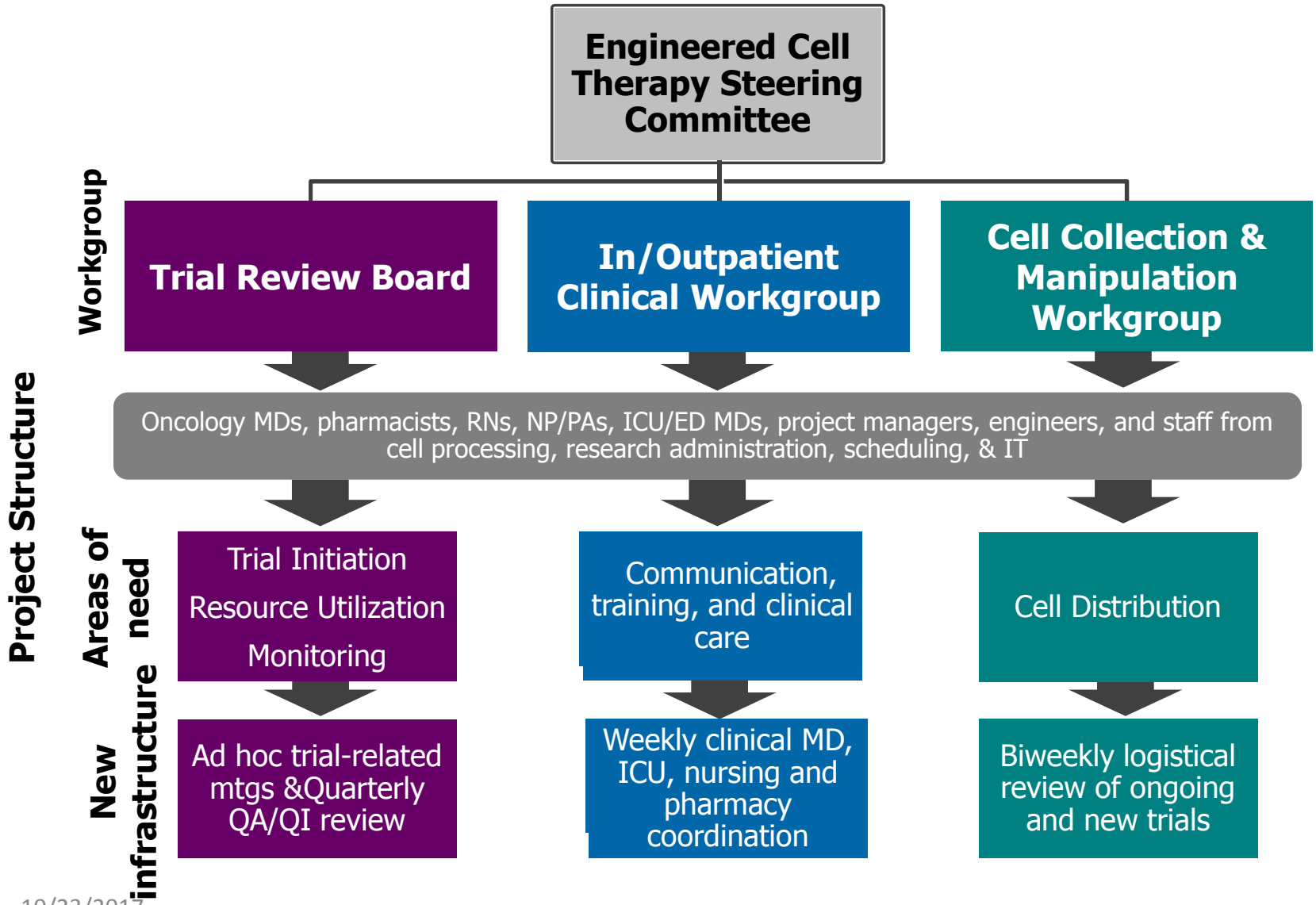
- Most requirements are **common to any cellular therapy** or also applicable to HPC transplant
- Highlight unique aspects of administration and toxicities:
  - **Third-party manufacturers**
  - **Cytokine release syndrome** and other adverse events
  - **Coordination** among different departments
  - Data management

Foundation for the Accreditation of Cellular Therapy

Engineered T Cell Scenarios



Infrastructure - Safety, Multidisciplinary, Coordination, Oversight



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Challenge:

Product shows up on manufacturing facility's door!

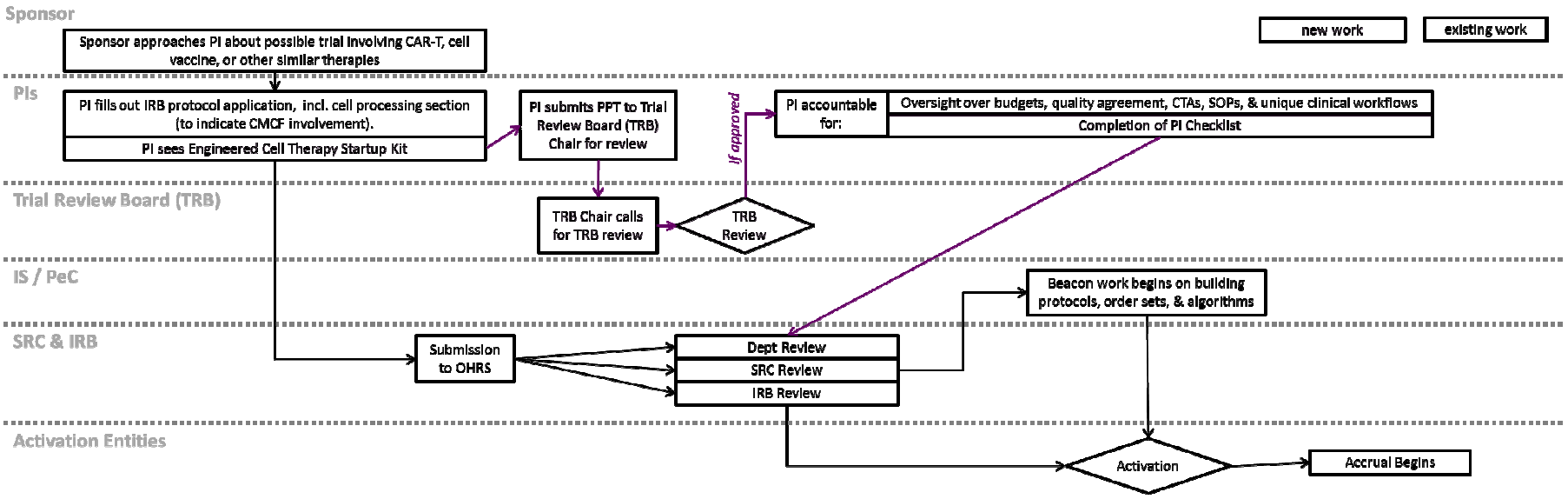
No warning, no context, no involvement in activation process

No inclusion in budget

Solution:

Modification of IRB submission work flow

Educational tools and accountability



Example of OHRS Guidance for Trial Teams

ENGINEERED CELL THERAPY TRIAL REVIEW BOARD

☐ **Presentation of trial at Trial Review Board meeting.** Use PowerPoint presentation as a base. Email completed presentation to Rob Soiffer (copy Sarah Nikiforow). A date will be arranged for you to present.

REGULATORY

☐ **Submit PIBC application if infectious agent is involved (e.g. plasmid or viral vector).** Create an online account and submit once documents are final:

- Protocol
- IB
- ICF draft
- NIH/RAC approval

CMCF contacts are available for help if necessary. Contact Olive Sturtevant with questions.

☐ **Submit documents to DFCI Biohazard Control Committee.**

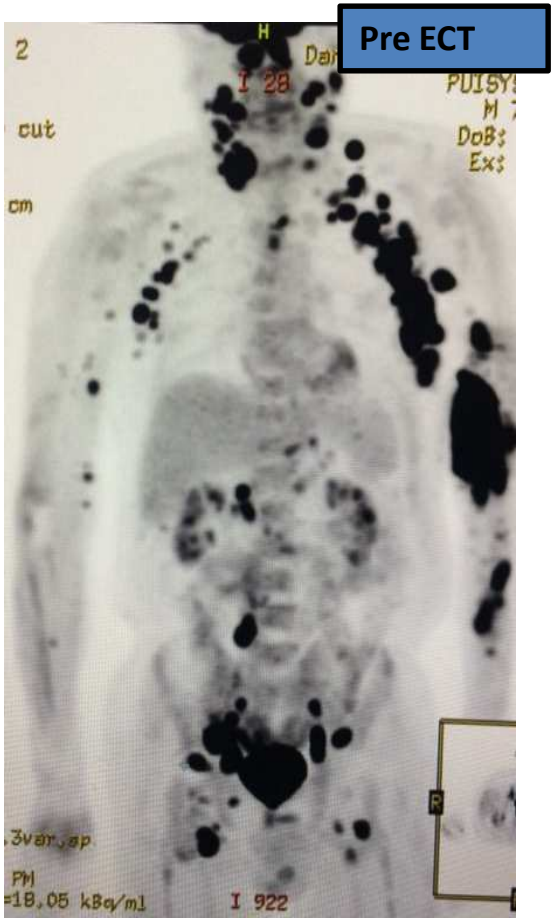
CONTRACTING

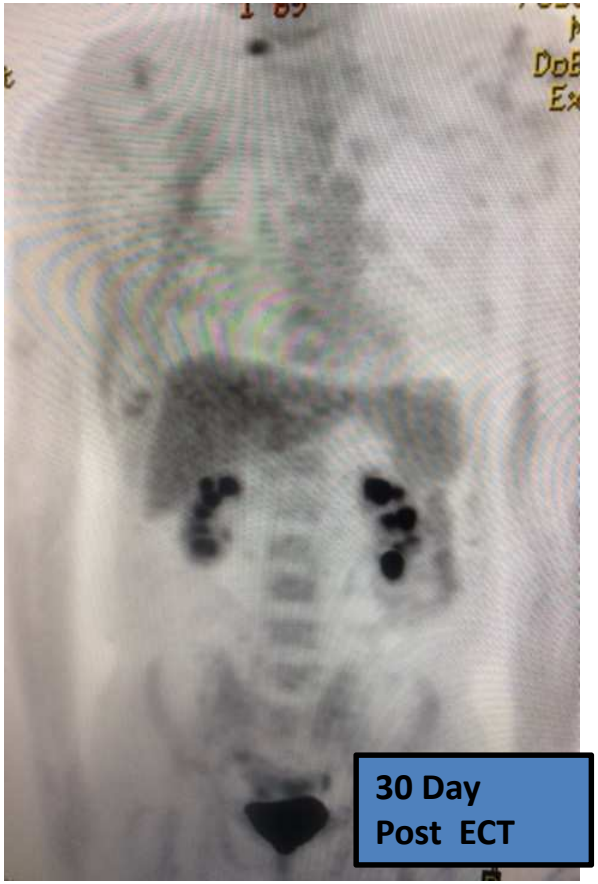
☐ **Ensure inclusion of role and budget for CMCF (processing) in DFCI Trial Agreement.**

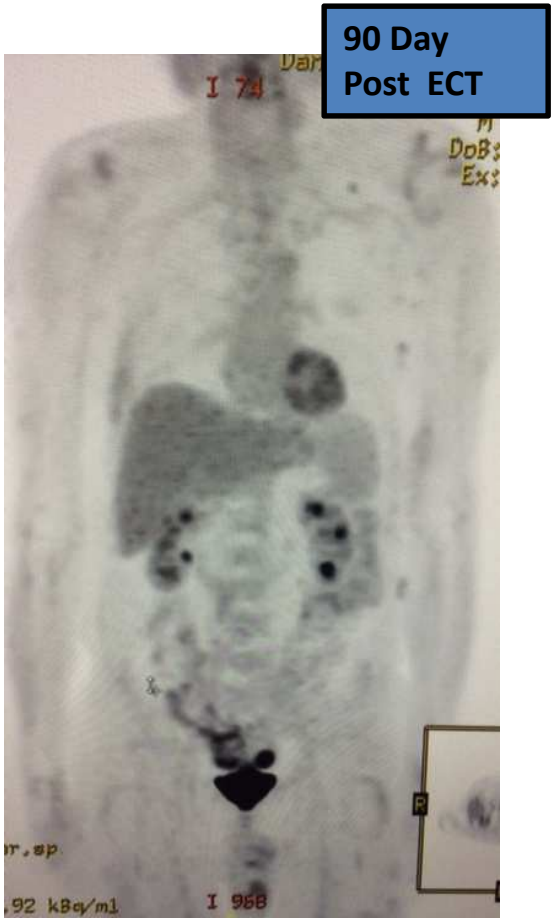
☐ **Ensure inclusion of role and budget for Kraft (apheresis) in DFCI Trial Agreement.**

☐ **Ensure grants and contracts are aware that this is an engineered cell therapy trial.** Discuss approach to chemotherapy, hospital admissions, and special medication required for management (SOC versus research).

Case Study #1







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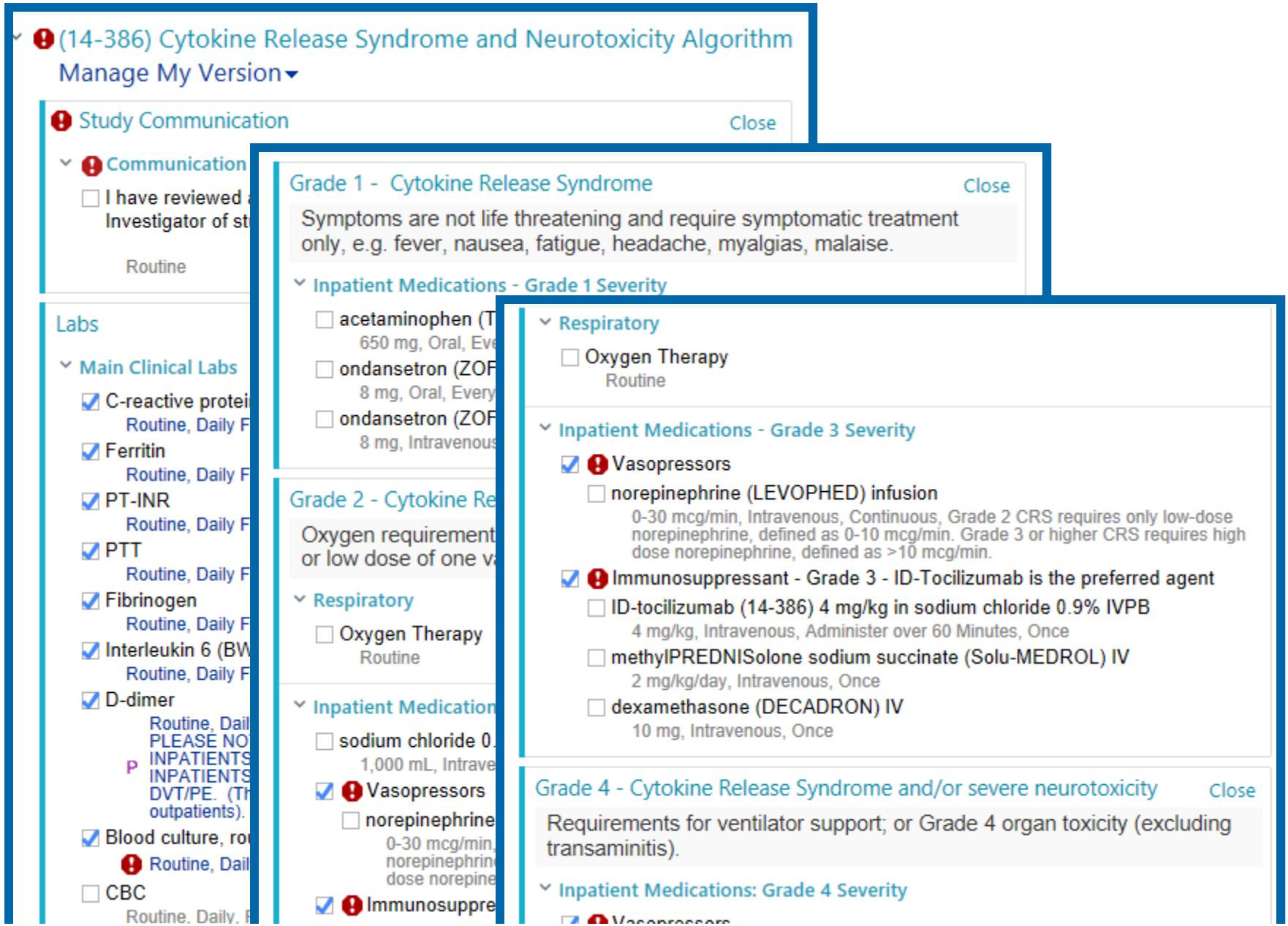
Demands of these Novel Cell Therapies

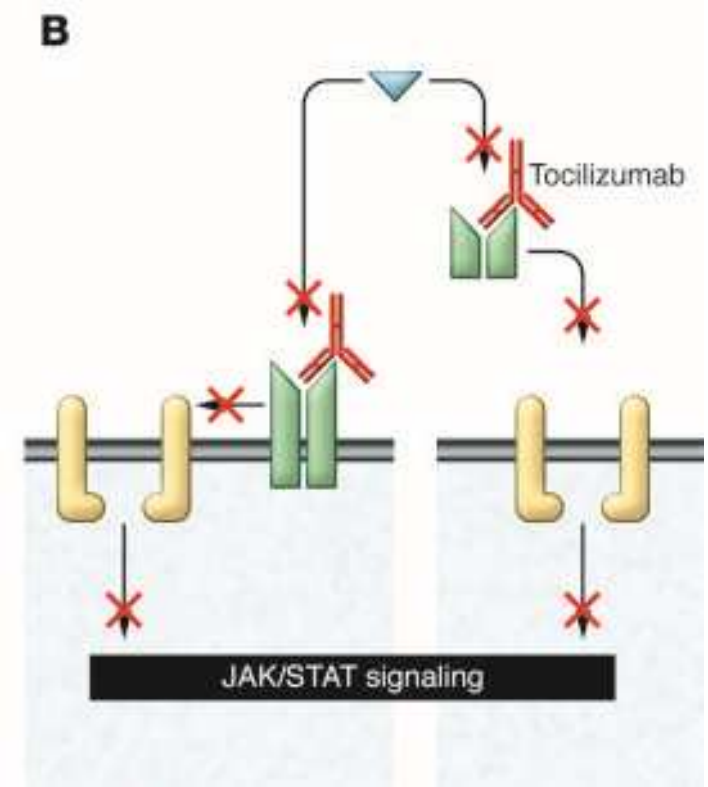
- Rapid Identification and Communication
  - On presentation in Emergency Department/clinic
  - On need to escalate care to ICU
  - Electronic Medical Record flags, email distribution lists, central list of "at risk" individuals

- Coherent Therapeutic Responses
  - Tocilizumab readily available
  - Institutional and protocol-specific order sets
  - Guidance and hyperlinks in admission notes/acute care plans

Each protocol has nuances for therapies of CRS – CONTACT PI IMMEDIATELY upon change in clinical status

Example of EPIC CRS Order Sets





Challenge:

Tocilizumab is only on outpatient pharmacy formulary and physically accessible 9-5 Mon-Friday

Solution:

Added to inpatient formulary

Weekly MDs, RNs, pharmacy, and coordinators forum sharing clinical events and upcoming needs.

Conclusions

- Cellular Therapy is expanding in scope and complexity
- In implementing clinical trails, identifying “pain points” in labelling in communication both under sponsor and institution control are key.
- Specifically in the hematologic malignancies, CAR-T cell therapies are exploding…with impact of commercialization yet to be seen
- Clinical delivery and care systems are needed to deliver each unique product safely, effectively, and to regulatory agency standards.

Enjoy the adventure!